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SHORT REPORT

Safety of bivalent human papillomavirus vaccine in the US vaccine adverse event reporting system (VAERS), 2009–2017

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AIMS

Human papillomavirus (HPV) vaccines prevent infection with oncogenic virus types. We analysed reports to the US Vaccine Adverse Event Reporting System (VAERS) of adverse events (AE) following bivalent HPV vaccine (2vHPV).

METHODS

We conducted descriptive analysis of 2vHPV reports, reviewed individual reports, calculated crude AE reporting rates and conducted empirical Bayesian data mining.

RESULTS

Of 241 2vHPV reports, 158 were in females, 64 in males (2vHPV is approved for females only) and 19 with unknown sex; 95.8% were classified as nonserious. Dizziness, headache, nausea and injection site reactions were the most common symptoms. Crude AE reporting rates were 33.3 reports per 100 000 doses distributed overall, and 1.4 per 100 000 for serious reports. Empirical Bayesian data mining identified disproportional reporting for three types of medical errors; assessment indicated findings that were probably driven by inadvertent 2vHPV use in males.

CONCLUSIONS

We did not identify any new or unexpected safety concerns in our review of 2vHPV reports to VAERS.

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Introduction

Human papillomavirus (HPV) bivalent (types 16, 18) vaccine [2vHPV, Cervarix, GlaxoSmithKline (GSK)] was licensed by the US Food and Drug Administration (FDA) in 2009 [1]. It is approved for use in females aged 9–25 years and is an HPV vaccine recommended by the Advisory Committee on Immunization Practices for females beginning at age 11 or 12 years, starting as early as 9 years [1]. 2vHPV, in a three-dose series, is indicated for prevention of diseases caused by oncogenic HPV types 16 and 18: cervical cancer, cervical intraepithelial neoplasia grade 2 or worse, adenocarcinoma *in situ*, and cervical intraepithelial neoplasia grade 1 [1].

2vHPV was not widely used in the USA (<2% of all HPV vaccines distributed during 2009–2017; personal communication, GSK) and the manufacturer stopped marketing it there in 2016. However, since 2014, 2vHPV has been licensed and used in at least 134 countries [2]. Data from prelicensure clinical trials and postlicensure safety monitoring indicate that injection site reactions, fever, headache, nausea, dizziness, malaise and syncope are commonly reported adverse events (AEs) following 2vHPV [3–5] – generally similar to the safety profile of the quadrivalent HPV vaccine [6]. We conducted a review of reports submitted to the US Vaccine Adverse Event Reporting System (VAERS) following 2vHPV from 2009–2017 to add to the body of knowledge on its safety.

Methods

VAERS is a spontaneous (i.e. passive) reporting system for AEs following vaccination [7]. It is coadministered by the Centers for Disease Control and Prevention (CDC) and the FDA and accepts reports from healthcare providers, manufacturers, and the public. Signs and symptoms of AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) terms [8]. Reports are classified as *serious* based on the US Code of Federal Regulations and definitions by the International Conference on Harmonization if any of the following are documented: hospitalization; prolongation of existing hospitalization; permanent disability; life-threatening illness; congenital anomaly; or death [9, 10]. Medical records are requested for serious reports. VAERS is used to conduct routine public health surveillance and is not subject to Institutional Review Board review and informed consent requirements.

We searched the VAERS database for reports following 2vHPV for persons vaccinated from 2009–2017, with reports received by 31January 2018, to account for data lags. We excluded foreign source reports because most are submitted by vaccine manufacturers and reporting requirements for their foreign source reports are different from their US reports. Therefore, foreign source and US reports may not be broadly comparable on important characteristics. We conducted descriptive analysis and reviewed each individual report. We calculated crude AE reporting rates based on the number of 2vHPV doses distributed in the USA during the analytic period. Crude AE reporting rates are presented as reports per 100 000 2vHPV doses distributed. We conducted empirical Bayesian data mining using established methods [11, 12] to identify 2vHPV-AE pairs reported at least twice as frequently as expected [i.e. lower bound of the 90% confidence interval surrounding the empirical Bayesian geometric mean (EB05 > 2)] compared to all other US-licensed vaccines in the VAERS database. We did not analyse 2vHPV data by dose number as this information is often missing or inconsistently reported.

Results

During the analytic period, VAERS received 241 US reports following 2vHPV; 158 in females, 64 in males (2vHPV is not approved for or recommended in males), and 19 with sex not reported or unknown (Table 1).

Among the 158 reports in females, 149 (94.3%) were nonserious and 93 (58.9%) were in persons aged 11–17 years; in 32 reports (20.3%), age was not reported or unknown. Median time from vaccination to symptom onset was 0 days (the day of vaccination) and ranged up to 2.5 years. Most reports were submitted by healthcare providers (38.6%) and manufacturers (34.8%; Table 1). In 97 (61.4%) reports, 2vHPV was given alone. In the 61 reports involving 2vHPV coadministered with other vaccines, commonly reported concomitant vaccines included meningococcal conjugate (n = 39); tetanus and diphtheria (Td), or Td and pertussis (n = 32); and varicella (n = 17). Dizziness, headache, nausea and injection site reactions (e.g. pain, swelling and erythema) were commonly reported symptoms (Table 2). Nine reports in females were classified as serious: (i) Guillain-Barré syndrome (symptom onset 37 days after vaccination and also preceded by a salmonella infection [date unspecified]); (ii) spontaneous abortion (2vHPV is not recommended in pregnancy); (iii) viral gastrointestinal infection; (iv) influenza-like symptoms; (v) abdominal pain; (vi) altered mental status; (vii) optic neuritis; (viii) postural orthostatic tachycardia syndrome; and (ix) vomiting, headache and mydriasis. There was one nonserious report of complex regional pain syndrome.

Among the 64 reports of males who received 2vHPV vaccine, median age was 13 years and symptom onset ranged from 0 to 226 days. Sixty-three (98.4%) were nonserious and the single serious report described fatigue, chills, cough, dehydration and back pain in a 14-year-old approximately 226 days after vaccine administration; the dose number in series was missing in this report. In 53 (82.8%) reports, 2vHPV was given alone. In the 11 involving 2vHPV coadministered with other vaccines; commonly reported concomitant vaccines included meningococcal conjugate (n = 8); Td or Td and pertussis (n = 3); influenza (n = 3); and hepatitis A (n = 3). Product use issue, wrong drug administered, interchange of vaccine products and drug administration error were commonly reported events (Table 3). In 18 of the male reports, only an administration error was documented, with no adverse health event.

Approximately 723 502 2vHPV doses were distributed in the USA during the analytic period (personal

Table 1

Characteristics of human papillomavirus bivalent vaccine (2vHPV) reports, Vaccine Adverse Event Reporting System, 2009–2017

Report characteristics	Female *n* (%)	Male[a] *n* (%)	Unknown sex *n* (%)	Total reports *n* (%)
Total reports	158 (65.6)	64 (26.6)	19 (7.8)	241
Serious reports[b]	9 (5.7)	1 (1.6)	0 (0.00)	10 (4.1)
2vHPV given alone	97 (61.4)	53 (82.8)	16 (84.2)	166 (68.9)
Type of reporter				
Healthcare provider	61 (38.6)	24 (37.5)	0 (0.0)	85 (35.3)
Manufacturer	55 (34.8)	8 (12.5)	18 (94.7)	81 (33.6)
Patient/parent	15 (9.5)	1 (1.6)	0 (0.0)	16 (6.6)
Other	27 (17.1)	31 (48.4)	1 (5.3)	59 (24.7)
Age groups (years)				
<9[c]	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.4)
9–10	2 (1.3)	0 (0.0)	0 (0.0)	2 (0.8)
11–17	93 (58.9)	26 (40.6)	0 (0.0)	119 (49.4)
18–25	23 (14.6)	3 (4.7)	0 (0.0)	26 (10.8)
>25[c]	7 (4.4)	0 (0.0)	0 (0.0)	7 (2.9)
Not reported or unknown	32 (20.3)	35 (54.7)	19 (100.0)	86 (35.7)
Adverse event onset (days)[d]				
Median (range)	0 (0–899)	0 (0–226)	0 (0–0)	0 (0–899)

[a]2vHPV is not approved for males
[b]Includes death, life-threatening illness, hospitalization, or prolongation of existing hospitalization, permanent disability or congenital anomaly as defined in 21CFR600.80 [8]
[c]2vHPV is not approved for these age groups
[d]Onset interval in days from time of vaccination (day 0) to first adverse event symptoms

communication, GSK). With 241 total 2vHPV reports (231 nonserious and 10 serious), crude AE reporting rates were 33.3 per 100 000 doses distributed overall, 31.9 per 100 000 for nonserious reports, and 1.4 per 100 000 for serious reports. After factoring out the suspected administration error reports where no AE was documented (213 nonserious and 10 serious), crude AE reporting rates were 30.8 per 100 000 doses distributed overall, 29.4 per 100 000 for nonserious reports and 1.4 per 100 000 for serious reports.

MedDRA preferred terms *product use issue*, *wrong drug administered* and *interchange of vaccine products* exceeded the empirical Bayesian data mining threshold (EB05 > 2) and were not previously identified and characterized events associated with 2vHPV. Review of reports indicated findings were driven by inadvertent 2vHPV use in males (i.e. administration errors).

Discussion

The results of our analysis of AEs reported to VAERS following 2vHPV are reassuring and are comparable to postlicensure safety data for the more commonly used (in the USA) quadrivalent HPV vaccine (4vHPV). Overall, 95.8% of reports were nonserious, similar to findings for 4vHPV (94.2%) [6]. Crude AE reporting rates for 2vHPV and 4vHPV vaccines – 33.3 per 100 000 doses distributed versus 32.7 per 100, 000 doses distributed, respectively – were also similar. Injection site reactions, dizziness and headache were common symptoms in 2vHPV reports. This is consistent with prelicensure clinical trial data and postlicensure surveillance from outside of the USA, and is also similar to findings for 4vHPV in a large postlicensure safety review in VAERS [2–6]. Our review of individual reports, which included cases of postural orthostatic tachycardia syndrome, Guillain–Barré syndrome and complex regional pain syndrome, did not reveal any unusual or unexpected patterns. Similarly, a review conducted by the European Medicines Agency found no evidence to support a causal association between HPV vaccines and postural orthostatic tachycardia syndrome or complex regional pain syndrome [13].

VAERS is a passive reporting system with limitations including under-reporting, incomplete data, and lack of an unvaccinated comparison group [7]. Due to limitations, we generally cannot determine if AEs are caused by vaccination from VAERS data alone. For example, the single serious male report with a delayed onset of 226 days for a constellation of nonspecific signs and symptoms calls into question a

Table 2

Most commonly reported adverse events[a] following human papillomavirus bivalent vaccine (2vHPV) in females, Vaccine Adverse Event Reporting System, 2009–2017

Female 2vHPV reports	***n* (%)**		***n* (%)**
Non-serious	**149**	**Serious[b]**	**9**
Dizziness	23 (15.4)	Headache	5 (55.6)
Headache	23 (15.4)	Pain	3 (33.3)
Injection site erythema	20 (13.4)	Nausea	2 (22.2)
Nausea	19 (12.8)	Grip strength decreased	2 (22.2)
Erythema	13 (8.7)[c]	Lumbar puncture	2 (22.2)
Female reports where 2vHPV was given alone	***n* (%)**		***n* (%)**
Nonserious	**90**	**Serious[b]**	**7**
Dizziness	23 (25.6)	Headache	4 (57.1)
Headache	23 (25.6)	Mydriasis	2 (28.6)
Injection site erythema	20 (22.2)	Grip strength decreased	2 (28.6)
Nausea	19 (21.1)	Lumbar puncture	2 (28.6)
Erythema	13 (14.4)[c]	Multiple MedDRA preferred terms with *n* = 1	1 (14.3)

[a]Based on Medical Dictionary for Regulatory Activities (MedDRA) preferred terms; a single report may be assigned more than one MedDRA preferred term (i.e. not mutually exclusive); MedDRA preferred terms for laboratory values are not included
[b]As defined in 21CFR600.80 [8]
[c]Other MedDRA preferred term with *n* = 13: urticaria

Table 3

Most commonly reported adverse events[a] following human papillomavirus bivalent vaccine (2vHPV) in males, Vaccine Adverse Event Reporting System, 2009–2017

Male 2vHPV reports	***n* (%)**		***n* (%)**
Nonserious	**63**	**Serious[b]**	**1**
Product use issue	22 (34.9)	Arthralgia, asthenia, asthma, and other MedDRA preferred terms	1 (100.0)
Wrong drug administered	20 (31.8)		
No adverse event	18 (28.6)		
Interchange of vaccine products	5 (7.9)		
Drug administration error	3 (4.8)		
Male reports where 2vHPV was given alone	***n* (%)**		***n* (%)**
Nonserious	**53**	**Serious[b]**	**0**
Product use issue	22 (41.5)		
Wrong drug administered	20 (37.7)		
No adverse event	18 (34.0)		
Interchange of vaccine products	5 (9.4)		
Drug administration error	3 (5.7)		

[a]Based on Medical Dictionary for Regulatory Activities (MedDRA) preferred terms; a single report may be assigned more than one MedDRA preferred term (i.e. not mutually exclusive); MedDRA preferred terms for laboratory values are not included
[b]As defined in 21CFR600.80 [8]

plausible biological relationship. Furthermore, estimates of crude reporting rates using doses of 2vHPV vaccine distributed should be interpreted with caution, since the actual numbers of doses administered are unknown. Despite these limitations, VAERS is a valuable monitoring system to detect potential vaccine safety problems that might require further investigation using controlled studies.

Our analysis is the first VAERS postlicensure safety assessment focused on 2vHPV and adds to the existing body of evidence on the safety of 2vHPV. We did not identify any new or unexpected safety concerns in our review of 2vHPV reports to VAERS from 2009–2017. The relatively high number of reports in males, for whom 2vHPV is not approved, and disproportional reporting for vaccine administration errors in males compared to other vaccines suggests some healthcare provider lack of awareness of FDA-approved indications and Advisory Committee on Immunization Practices recommendations.

Implications and contribution

Human papillomavirus (HPV) causes certain cancers in women and men. HPV vaccines are highly effective in preventing infection with oncogenic HPV types. However, safety concerns have contributed to vaccine hesitancy. Our review of postlicensure safety data of the bivalent HPV vaccine did not identify any new or unexpected safety concerns, which may provide reassurance to patients, parents and healthcare providers.

Competing Interest

There are no competing interests to declare.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC or the US FDA. Mention of a product or company name does not constitute endorsement by the CDC or FDA. Information on Cervarix doses distributed is presented with the permission of GSK.

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